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ART UNIT	PAPER NUMBER
1802/1115	9

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DATE MAILED: 11/15/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/8/94 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☒ Interview Summary.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-10 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-10 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

III. DETAILED ACTION

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure and failing to adequately describe the instant invention.

The specification provides the competitive inhibition of the binding of cobalbumin to intrinsic factor. In addition, the instant specification adds the data of figure 2 which purports to show a first order dissociation rate of antibody from intrinsic factor. Applicants urge that the spike and subsequent dissociation in a concentration dependent fashion relates to the competition between the antibody-intrinsic factor in dynamic equilibrium and the B12-intrinsic factor in dynamic equilibrium. Thus, the results of figure two would seem to buttress the conclusion that the 585.3A3A8 antibody merely binds at the binding site to B12-intrinsic factor or in a manner that sterically hinders the binding.

The response filed 8/8/94 states that the data provided in fig. 2, newly submitted in the instant CIP filing is sufficient to establish a ternary Ab-IF-B12 complex. See page 3, top, of 8/8/94 response. However, such an argument fails to account for the fact that the affinity of B12 for IF could be different than

the affinity of antibody for IF. Since the Ab and B12 are different molecules, the affinities of the both B12 and Ab are likely different. Under such conditions, the B12 would compete for a binding site with the antigen. In such a situation, the affinity of antibody for antigen, in this case IF, could be superseded by the affinity of B12 for antigen, IF. Then the B12 would replace the antibody at a common binding site. As such, the binding site of antibody and antigen would be the same. The fact that the antibody of the preferred embodiments happens to bind to intrinsic factor only in the absence of B12 may also be attributed to an epitope which is occluded by binding of B12 to IF. Applicants urge at page 2, paragraph 5, that, should the B12 binding site and antibody binding sites be the same, the dissociation rate of IF/antibody would be largely unaffected by the concentration of B12 and that the B12 would not be able to "bump" the antibody off IF. This statement is not agreed with. If the affinity of B12 for IF is higher than antibody for IF, then B12 will indeed "bump" the antibody off and the IF binding will be dependent on the concentration of B12. An objective example of such a reaction is an affinity purification technique where the antibody is eluted from a column by solvent containing an excess of antigen. In such a situation, as in applicant's BIAcore, the solvent is flowing and presumably any unbound antibody would not flow away.

In conclusion, the rejection is being maintained because applicants have not established that the alleged "allosteric" binding mechanism hypothesized by the specification indeed exists. The previous application merely set forth competitive binding data which was completely inconclusive. The present specification is not much more complete. New data in figure two purports to show concentration dependent dissociation of antibody from IF. In view of the foregoing discussion of the insufficiency of the data presented by applicants, the specification fails to teach how to use the invention as disclosed. Applicants have disclosed an invention which is disclosed to have a certain activity and are asserting that their invention contains all derivatives that have said certain activity. To support such a disclosure, applicants have provided a single disclosed antibody. Undue experimentation would be required to extrapolate the preferred embodiment to any and all antibodies containing this function because applicants have not provided the routineer with the necessary guidance enabling said routineer to obtain other antibodies having the same binding activity. Considering the fact that applicants have not conclusively established the disclosed utility (ie. allosteric binding activity) for the preferred antibody, adequate guidance clearly does not exist for any antibody containing allosteric binding activity. Accordingly, undue experimentation would be required to practice the invention

as described. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. Appls. & Int. 1986).

The description on pages 13 and following of the generation of intrinsic factor antibodies is of a relatively generic nature. Specifically, no particular peptide or epitope is set forth that would teach one of ordinary skill in the art how to reproducibly obtain applicant's preferred embodiments. Note, for example, the use of conventional, commercially available reagents at the bottom of page 14, top of page 15. Because of such general disclosure, the specification lacks teaching of the critical elements necessary to produce the preferrred 585.3A3A8 as opposed to any other antibody. Without such guidance, the specification is deficient in teaching how to make the invention. Accordingly, deposit is required of applicant's 585.3A3A8 antibody to insure availability and viability. See 37 C.F.R. 1.801-1.809.

In the response filed 8/8/94, page 4, para. 4, applicants state that the hybridoma has been deposited under a given ATCC deposit number. However, the statement does not contain a guarantee of availability to the Commissioner upon request during the pendency of the instant application. In addition, the statement contains no guarantee that the restrictions to the availability of the hybridoma will be irrevocably removed upon issuance of a patent from the instant application. Finally, no guarantee of viability for the longer of 30 years or 5 years from

the date of the last request is provided. Accordingly, absent a sworn statement averring to the foregoing as provided in 37 C.F.R. 1.801-1.809, the objection is maintained.

17. Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

18. Claims 2-8 are rejected under 35 U.S.C. § 103 as being unpatentable over Galfre' in view of Chen.

The claims presently recite a generic kit and method of producing a monoclonal antibody to intrinsic factor as well as generic methods of diagnosis. While a variety of actual steps are recited as are specific cell types, the particulars of the preferred embodiments merely recite a method of obtaining an antibody by traditional hybridoma means.

The Galfre reference provides teachings for the production of antibodies for any particular antigen. Note the reference at the beginning of the second paragraph. The only thing the reference is missing is the particular antigen.

This is provided by Chen. The reference discloses a radioassay using pure intrinsic factor. The presence of a pure antigen renders the antibody to that antigen to be obvious absent clear and convincing showing of unexpected properties in the resultant antibody. The reason for such a determination is that the manufacture of antibodies as of 1991, the priority date of

the instant application, was well known. Note the fact that the Chen and Galfre` references were published in 1981. Therefore, the art demonstrated that as much as 10 years prior to the priority of the claimed invention, antibodies specific for intrinsic factor were disclosed.

The instant rejection is being made essentially because the claims seem to be the recitation of method steps which are generic to hybridoma antibody production. Therefore, a generic reference to hybridomas was cited with a specific reference to the antigen in question used in combination to render the claims obvious. Should applicants traverse the rejection, the response should include discussion of exactly those elements in the claims which are not technologically obvious over generic hybridoma technology.

It is noted that the claims to the kit are merely a further recitation of the antibody and intrinsic factor to be used in a conventional immunoassay format, ie. bound to a solid support, etc.. Since the use of an antibody in an immunoassay kit would have been obvious to one of ordinary skill in the art, the patentability of the antibody is considered to determine the patentability of the kit. For example, the kit claims recite elements such as a solid support and the attachment of the antibody to the solid support which is conventional in the immunoassay art. For example, the sandwich of an antibody between

two antibodies is routine. Moreover, review of the invention disclosed in the specification indicates that the inventive concept is the antibody and the way said antibody binds to intrinsic factor, rather than the combination of the antibody with a kit. Accordingly, the rejection is directed towards the antibody.

Applicant's 8/8/94 response essentially argues that the art neither teaches or suggests the presence of allosterically binding antibodies. However, since the evidence and arguments presented are equally deficient, the rejection is maintained.

19. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Smolka.

The claim is broadly drawn in functional terms to an allosteric epitope on intrinsic factor. However, review of the specification to elucidate support for such a claim shows that the specification only provides competitive binding data. Applicants have chosen to interpret this data to mean that the claim antibody composition has allosteric binding affinity. However, the only evidence to support such a conclusion is the competitive inhibition data of figure 1. In the instant filing, applicants have submitted a separate figure 2 which purports to provide dissociation rate data showing first order dissociation. Additionally, the rate of dissociation is directly proportional to the amount of B12 present in solution. The rate of

dissociation in a normal first order rate graph shows a linear result plotting ln c/c_0 against time. The data provided only shows a "relative response" without clearly explaining what this parameter is or to what it is relative. Moreover, the x axis does not show time, it shows "seconds in dissociation phase" which does not provide the requisite time. Therefore, applicant's data does not adequately support the statement in the specification at page 22, line 8, that the dissociation is first order. Accordingly, the current rejection is maintained under the conclusion that the claims merely provide data which shows competitive binding between B12 and IF.

Smolka disclose monoclonals to intrinsic factor. Since Smolka teaches a monoclonal antibody having a binding activity where the antibody can only bind intrinsic factor in the absence of B12, the claims are anticipated.

It is noted that the specification does not actually show the argued embodiments of allosteric binding to intrinsic factor, only competitive binding is disclosed. Note, for example the abstract at line 11 where cobalbumin binding is inhibited by the claimed antibodies. Notice also the teaching in Smolka where five antibodies were capable of inhibiting the binding of Cobalbumin to IF. Therefore, the embodiments are still considered to be met by the prior art and the antibody in the Smolka reference is considered to be the same as applicants'. That evidence is the

competitive binding assay set forth in example 6 and figure 1. As concentration of B12 increases, the luminescence decreases. The competitive binding disclosed by Smolka at page 609, top of the left column is the same evidence presented by applicants. Accordingly, the reference is anticipatory.

In addition, applicant's new experiment set forth on page 22 of the instant specification does not overcome the instant rejection under §102 because the supplemental experiment is merely further characterization of the claimed invention. Such an experiment does not serve to distinguish the claimed antibody from the prior art. To completely distinguish their invention from the prior art, applicants are invited to present side-by-side comparison showing that the binding characteristics of the claimed antibody are different from that of the prior art. Otherwise, no evidence exists of record to show that the prior art antibody would not inherently contain the allosteric characteristics claimed by applicants.

Applicants urge in the 8/8/94 response that the reference neither discloses or suggests an allosteric antibody. However, because applicant's evidence are similarly deficient, the arguments are not persuasive and the rejection is maintained.

20. Claims 9-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Ellis et al.

The rejected claims are drawn to a generic method of assaying for the presence of B12 in a sample by contacting said sample with intrinsic factor and antibody bound to a support. The Ellis reference teaches a generic method of binding antibody which blocks the binding of intrinsic factor to B12. The limitation of claim 10 to monoclonal antibodies is considered obvious as the generation of monoclonal antibodies from polyclonal antibodies was considered obvious in 1991. Note the dates of Chen and Galfre' concerning the availability of antibodies to intrinsic factor 10 years prior to the priority date which establishes that these antibodies and methods were well established in the art. Additionally, the Galfre' reference teaches the manufacture of monoclonal antibodies. Finally, applicant's attention is directed to *Ex parte Ehrlich*, 3 USPQ2nd 1011 (BPAI, 1987). Accordingly, the claimed diagnostic assay is considered obvious as is the substitution of bound antibody for bound intrinsic factor. Note especially the teaching in the reference at col. 2, lines 30 and following. The reference teaches the isolation of B12/intrinsic factor complexes from antibody/intrinsic factor complexes. Moreover, the claims also recite more particularly the intrinsic factor attached to a support. The claimed method is merely substitution of an antibody for intrinsic factor on the support. Since the two exist in dynamic equilibrium where constant association dissociation

occurs, the substitution of bound intrinsic factor for bound antibody is considered to be an obvious variation.

Applicants have argued in the 8/8/94 response that the substitution of antibody for intrinsic factor on the solid support is not present within the reference. In response, see col. 3, lines 44 and following where receptor substrates can be attached to the support. Insofar as the substitution of receptors for antibodies as argued bridging pages 6 and 7 of the 8/8/94 response is concerned, the reasons that antibodies and receptors can be interchanged for the purpose of the Ellis reference is as follows. First, antibodies act as cellular receptors in naive B cells (IgM). Second, the function of antibodies and antigens is the same in the invention as claimed and that function is to bind ligand. Accordingly, because antibodies can act in the same way as receptors, the substitution of antibodies for receptors in the Ellis patent is considered obvious.

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). c76E

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22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Nisbet whose telephone number is (703) 308-4204 from 9:00 am to 5:00 pm weekdays with the exception of alternating Fridays. Lf the examiner cannot be reached, the supervisor may be contacted at phone number (703)308-3535.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TMN
January 9, 1994

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
1/10/94